REMARKS/ARGUMENTS

Applicant acknowledges the Examiner's decision to rejoin the claims in Groups I and II of the restriction requirement (Claims 1-11 and 49 and Claims 12-15, respectively) and the Examiner's decision not to rejoin the other groups. Applicant also acknowledges the Examiner's withdrawal of certain claims as being part of a nonelected species and the Examiner's note that Applicant will be entitled to consideration of claims to additional species upon allowance of a generic claim.

Information Disclosure Statement

Applicant acknowledges that the Girard and Hirth reference, which is in French and was cited in the information disclosure statement, was not considered because the information disclosure statement did not include a concise explanation of the relevance of the publication.

Rejection under 35 U.S.C. § 112

Claims 1-4, 9-15 and 49 were rejected under 35 U.S.C. § 112 as being indefinite. Applicant has made the changes requested by the Examiner, except for the change to the verb tense of the word "consist" in Claim 1. The Examiner noted that the verb appears to be of the wrong tense. Applicant respectfully disagrees, as the subject of the word "consist" is "linkers." In other words, each of the linkers in the library consists of a repeated pattern of degenerate repeated triplet nucleotides.

Rejection under 35 U.S.C § 102 and § 103 in light of Cwirla

* *The Cwirla Reference*

Claims 1-4, 9, 12, 13 and 49 are rejected under 35 U.S.C. §102 (a,b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Cwirla *et al*, Proc. Nat'l Acad. Sci. USA, 87:6378-6382 (1990).

Under 35 U.S.C. Section § 102, to anticipate a claim, a reference must disclose each and every element of the claim. See also MPEP § 2131. Claims 1-4, 9, 12 and 13 recite (i) "a first and second domain" and Claim 49 recites (ii) a library of linkers, each of which "joins two nucleic acid domains or two nucleic acid sequences encoding two polypeptide domains." The term domain used in conjunction with polypeptides is defined on page 11 of the specification as "a region of a polypeptide chain that is folded in such a way that confers a particular structure and/or biochemical function." When the term "domain" is used in conjunction with nucleic acids, it refers to a nucleic acid that encodes a polypeptide domain, as that term is defined in the specification, or a nucleic acid structure that carries out a particular function. Finally, the specification on page 14, lines 3-5 defines the term "linker," when used in terms of a nucleic acid, as "a nucleic acid molecule or sequence that joins two nucleic acid domains or two nucleic acid sequences encoding two polypeptide domains." .

Cwirla fails to disclose a first and second domain. The variable region in Cwirla, which the Examiner equates to the linker of the present invention, is situated between a nucleic acid sequence that encodes a signal peptide and a nucleic acid sequence that encodes a phage adsorption protein. A signal peptide is not a domain, as that term is

defined in the specification. Therefore, Cwirla does not disclose a "first and second domain" as recited in Claims 1-4, 9, 12 and 13. Nor does the variable region in Cwirla "join two nucleic acid domains or two nucleic acid sequences encoding two polypeptide domains," as is required by Claim 49. Finally, the variable region of Cwirla is not a linker as that limitation is used in Claims 1-4, 9, 12 and 13 and defined in the specification.

Claims 1-4, 9, 12 and 13 each include as a limitation "a randomized library of linkers that vary in size and nucleotide sequence." Even if the variable region of Cwirla could be considered a linker, which it cannot, the Cwirla variable region only varies in nucleotide sequence but not in length, as shown in Figure 4, on page 6381, for example. For all of the above reasons, Cwirla does not anticipate Claims 1-4, 9, 12 and 13, and Applicant respectfully requests withdrawal of this rejection.

Claims 1-4, 9, 12, 13 and 49 were also rejected as obvious in light of Cwirla. To establish a *prima facie* case of obviousness, (i) the prior art reference must teach or suggest all the claim limitations, (ii) there must be some motivation or suggestion to combine the references, and (iii) there must be a reasonable expectation of success. See MPEP § 2142, "Establishing a *prima facie* case of obviousness." As described above, the Cwirla reference does not teach or suggest all of the claim limitations. In addition, Cwirla would not motivate one of ordinary skill in the art to vary a linker sequence. The variable region in Cwirla does not encode a linker, as that term is defined in the specification, but a peptide ligand that is presented to a particular receptor for binding in a phage display system. Therefore, a *prima facie* case of obviousness has not been

established based on Cwirla, and Applicant requests that this rejection be reconsidered and withdrawn.

Rejections under 35 U.S.C. §103

Claims 1-4, 9, 12, 13 and 49 were also rejected under 35 U.S.C. § 103(a) as being obvious over Holliger (U.S. Patent No. 5,837,242), Keck (U.S. Patent No. 6,040,431) and Dower (International Publication WO 91/19818). As noted above, to establish a *prima facie* case of obviousness, the prior art reference must teach or suggest all the claim limitations, there must be some motivation or suggestion to combine the references, and there must be a reasonable expectation of success. See MPEP § 2142, "Establishing a *prima facie* case of obviousness."

* *Claims 1-4, 9, 12, and 13 in light of Holliger, Keck and Dower*

Because the cited references do not, together or separately, disclose all of the limitations of claims 1-4, 9, 12 and 13, they do not render these claims obvious. The Holliger patent discloses using a linker to join binding regions of immunoglobulin variable regions such that they may form diabodies. The patent notes use of linkers of various lengths and provides guidelines for the *a priori* design of a certain linker to achieve a certain effect. As the Examiner notes, however, the Holliger patent does not disclose a randomized library of linkers that differ in both length and sequence, as set forth in Claims 1-4, 9, 12 and 13.

The Keck patent does not remedy the shortcomings of Holliger. The Examiner notes that Keck teaches "single chain constructs, termed morphons...which are regions of TGF beta superfamily proteins, that are linked by linkers..." The patent mentions creating a library of morphons with different linker regions, but it provides several *a*

priori considerations for engineering such linker regions, teaching away from creating a randomized library of linkers. For example, the section entitled "Polypeptide Linker Considerations" discloses guidelines for generating linkers that will maintain the tertiary structure of each peptide subunit, such as avoiding cysteine residues, using a Gly_4Ser or Ser_4Gly repeat, or using a computer algorithm to predict amino acid sequences that would be suitable to join heel and finger regions of a morphon peptide. (See columns 29-30 of Keck.) Keck does not suggest using a repeated pattern of degenerate repeated triplet nucleotides to obtain a *randomized* library of linkers that vary in sequence and length, as recited in Claim 1-4, 9, 12 and 13.

The Examiner asserts that the Dower application remedies the deficiencies of Keck and Holliger by disclosing a peptide library obtained with a variable codon region, such as $(NNK)_x$ or $(NNS)_x$. But the variable coding region of Dower, rather than encoding a variable linker region that joins two domains, encodes for peptides of interest that are presented to various receptors as ligands in a phage display system. See page 4, lines 4-21.

Moreover, Dower teaches away from using this variable coding region as a linker for two peptide domains. Dower discloses joining two variable coding regions with a constant linker region that is pre-engineered to achieve a certain purpose; namely, causing the peptides encoded by the variable coding region to be presented to the receptor in different ways. See page 13, lines 32-37 and pages 14-15 of Dower. Therefore, it is plain that Dower does not even contemplate use of its library for a linker region and would not provide inspiration for one of ordinary skill in the art to randomize, for example, the pre-engineered linkers of Holliger or Keck to form a library.

In addition, in Dower's libraries of peptide ligands the variable region differs in sequence but not in length, as the variable x in $(NNK)_x$ or $(NNS)_x$ remains the same for each particular library. For example, Dower notes on page 4 that in a preferred embodiment the oligonucleotide library member encodes a hexapeptide. Dower does not enable a single library with a variable region that varies in both length and sequence. Therefore, the library of Dower, in addition to encoding peptide ligands rather than peptide linkers, is not randomized in the same way as is the invention as claimed. For all of the reasons cited above, Holliger, Keck and Dower, taken alone or together, do not render obvious Claims 1-4, 9, 12 and 13.

** Claim 49 in light of Holliger, Keck and Dower*

The Holliger, Keck and Dower references also do not render Claim 49 obvious. Claim 49 recites a library of linker nucleic acid molecules or sequences "each of which joins two nucleic acid domains or two nucleic acid sequences encoding two polypeptide domains" in which each linker has a pattern of degenerate repeated triplet nucleotides with certain properties. As discussed above, Holliger does not teach a library of linkers but rather discloses certain linkers to be used in a particular context. Keck does not teach a library of linkers that have a certain pattern of degenerate repeated triplet nucleotides but rather linkers that may be used to link regions of TGF beta superfamily proteins and that are based on certain structural considerations that prevent destruction of the tertiary structure of these peptide regions.

Dower does not remedy these deficiencies, as it does not disclose a library of *linker* nucleic acid molecules, such as that recited in Claim 49 but rather a library of variable coding regions that encode peptide domains that are presented to various

receptors in a phage display system. Dower provides no motivation to use its library as a source for a linker region that joins two domains. The part of the application that mentions spacers (or linkers) for joining two variable peptide domains teaches spacers that are pre-engineered to have certain properties that affect the way the variable peptide domains of the library are presented to the receptors. Thus, such linkers do not comprise a library with the pattern recited in Claim 49.

In addition, the variable coding regions in Dower do not consist of a pattern of degenerate repeated triplet nucleotides in which position 1 cannot be the same as position 2, position 2 cannot be the same as position 3 and position 1 cannot be the same as position 1, as recited in Claim 49. The base nucleotide sequence in Dower is NNK or NNS, which violates the above claim limitations. Dower provides no motivation to change one of the N's to another degenerate nucleotide. For all of the reasons cited above, the Holliger, Keck and Dower references do not render Claim 49 *prima facie* obvious, as they do not disclose, either together or alone, all of the claim limitations of Claim 49.

* *Claims 10, 11, 14 and 15 in light of Holliger, Keck, Dower, and Turpen*

Claims 10, 11, 14 and 15 were rejected under 35 U.S.C. § 103(a) as being obvious over Holliger, Keck, Dower and Turpen (WO 96/12028). As noted above, the claims from which Claims 10, 11, 14 and 15 depend are not *prima facie* obvious in light of Holliger, Keck and Dower because these references do not, alone or together, disclose all of the limitations of the claims. Turpen does not remedy the deficiencies of the above references because it does not disclose randomized libraries of linkers that vary in length and sequence. Therefore, the claims at issue are not obvious in light of the above

references, and Applicant respectfully requests reconsideration and withdrawal of this rejection.

** Claims 10, 11, 14 and 15 in light of Cwirla and Turpen*

Claims 10, 11, 14 and 15 were also rejected under 35 U.S.C. § 103(a) as being obvious over Cwirla in view of Turpen. As discussed in detail above, Cwirla does not disclose all of the limitations of the independent claims from which Claims 10, 11, 14 and 15 depend. Turpen does not remedy the deficiencies of Cwirla, as it does not disclose randomized libraries of linkers that vary in length and sequence and link a first and second domain. Therefore, the claims at issue are not obvious in light of the above references, and Applicant respectfully requests reconsideration and withdrawal of this rejection.

Double Patenting Rejection

The Examiner also provisionally rejected Claims 1-4, 9-15 and 49 under the doctrine of judicially created obviousness-type double patenting as being unpatentable over Claims 54, 56, 60-64, 66, 67, 69, 72, 73, and 76-86 of co-pending Application No. 09/539,382. In response to this rejection, Applicant is willing to file a terminal disclaimer, either in the present case, or in Application No. 09/539,382, depending on which case is granted first. Applicant therefore requests that the Examiner postpone this requirement until one of the patent applications at issue is granted.

In light of the above amendments and remarks, Applicant believes that the application is in condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. Applicant does not believe any fees are required by this amendment, but if Applicant is mistaken, any required fees may be charged to deposit account 50-2767. If the Examiner has any questions regarding this communication, he is invited to contact the undersigned at (916) 444-3900, x353.

Respectfully submitted,

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